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METHOD FOR PREPARING 2-(SUBSTITUTED PHENYL) PROPIONALDEHYDE
[2-(Chikan Feniru) Propion Arudehido No Seizoho]

Eiji Takahashi, et al.

UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C. August 2004

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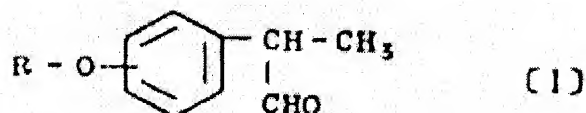
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TITLE	(54): METHOD FOR PREPARING 2- (SUBSTITUTED PHENYL) PROPIONALDEHYDE
FOREIGN TITLE	[54A]: 2-(Chikan Feniru) Puropon Arudehido No Seizoho

1. Title

METHOD FOR PREPARING 2-(SUBSTITUTED PHENYL) PROPIONALDEHYDE

2. Claims

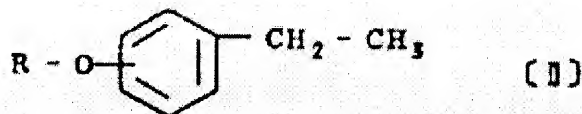
A method for preparing a 2-(substituted phenyl) propionaldehyde represented by General Formula [I]:



(in which R represents a phenyl group or a methyl group),

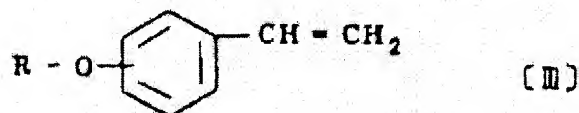
said method comprising the following process steps (I) and (II):

(I) a step of dehydrogenating a substituted phenyl ethane represented by General Formula [II]:



(in which R has the same meaning as defined in the foregoing)

at 400 to 700°C in the presence of a dehydrogenation catalyst so as to prepare a substituted phenyl ethylene represented by General Formula [III]:



(in which R has the same meaning as defined in the foregoing) and

(II) a step of reacting the aforesaid substituted phenyl ethane with hydrogen and carbon monoxide in the presence of a hydroformylation

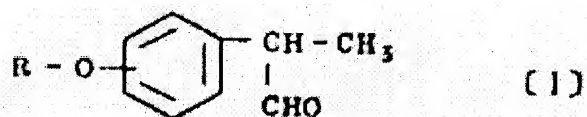
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catalyst so as to prepare the aforesaid 2-(substituted phenyl) propionaldehyde.

3. Detailed Description of the Invention

[Industrial Field of Application]

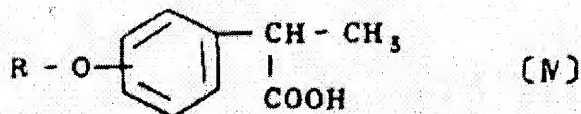
The present invention pertains to a novel method for economically preparing 2-(substituted phenyl) propionaldehyde represented by General Formula [I]:



(in which R represents a phenyl group or methyl group).

Many of the 2-(substituted phenyl) propionic acids represented by General formula [IV] below:

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(in which R has the same meaning as defined in the foregoing)

that are readily derived from 2-(substituted phenyl) propionaldehyde represented by General Formula [I], which is the target substance of the present invention, are useful as pharmaceuticals or intermediates thereof. For example, 2-(3-phenoxy phenyl) propionic acid, which, according to the method described in JP-A-S51-016636, JP-A-S54-039043, or the like, can be derived from 2-(3-phenoxy phenyl) propionaldehyde obtained by the method of the present invention, has anti-inflammatory, analgesic, and antipyretic effects and is known by its common name "fenoprofen."

[Prior Art]

Numerous methods have been proposed for the production of 2-(substituted phenyl) propionaldehyde represented by General Formula [I] and of 2-(substituted phenyl) propionic acid represented by General Formula [IV], and the following presents some representative processes:

1) a method for preparing 2-(substituted phenyl) propionic acid by reducing an acetophenone derivative having a substituent at the aromatic nucleus to convert it into 1-(substituted phenyl) ethyl alcohol and subsequently by subjecting the resulting alcohol to halogen substitution, cyanidation, and hydrolysis (see U.S. Patent No. 3,600,437 and JP-A-S58-077841),

2) a method for preparing 2-(substituted phenyl) propionic acid by reacting a phenyl acetic acid ester having a substituent at the aromatic nucleus with dialkyl carbonate, thereby converting it into a corresponding malonic acid diester, which is methylated with methyl iodide, subsequently hydrolyzed, and then decarbonated (see JP-B-S51-045586),

3) a method for producing 2-(substituted phenyl) propionaldehyde according to which a 3-methyl-3-(substituted phenyl) glycidic acid ester obtained by the reaction of an acetophenone derivative having a substituent at the aromatic nucleus and a monochloro acetic acid ester is treated with a mineral acid under a water-containing condition (see JP-B-S56-020239 and JP-B-S59-041976), and

4) a method for producing 2-(substituted phenyl) propionic acid or alkyl ester thereof according to which substituted phenyl ethylene obtained by dehydration or dehydrohalogenation of substituted phenyl ethyl alcohol or substituted phenyl ethyl halide is reacted with carbon dioxide and with a lower alcohol or water in the presence of a palladium-based catalyst (see JP-B-60-045171).

The substituted phenyl ethylenes represented by the aforesaid General Formula [III], which are the intermediate material in the method of the present invention, are phenoxy phenyl ethylenes or methoxy phenyl ethylenes. The most widely practiced method for producing this type of substituted phenyl ethylene having a phenoxy group or methoxy group as the substituent is a) dehydration or dehydrohalogenation of a corresponding substituted phenyl ethyl alcohol or substituted phenyl ethyl halide. For example, a method for producing 3-phenoxy phenyl ethylene by dehydration of 1-(3-phenoxy phenyl) ethyl alcohol is known (see JP-A-S53-018533). Other known methods include b) a method that employs decomposition of diaryl ethanes (see "Ind. Eng. Chem. Prod. Res. Develop.," 3(1), 16, 1964); c) a method that decomposes anisole having an alkyl group that has 3 or more carbon atoms, thereby obtaining 3-methoxy phenyl ethylene (see U.S. Patent No. 2,698,868); d) a method that decarbonates methoxy cinnamic acid (see "J. Applied Chem." 1, 95, 1951); e) a method that heats an acetophenone derivative having a substituent at the aromatic nucleus together with aluminum alkoxide (see JP-A-S49-086332); f) a

method that obtains 4-methoxy phenyl ethylene by oxidative dehydrogenation of 4-methoxy phenyl ethane, using carbonyl sulfide as the oxidizing agent (see U.S. Patent NO. 3,875,252); and so forth. However, there is no method that dehydrogenates phenyl ethanes having phenoxy groups or methoxy groups without the use of an oxidizing agent and thereby obtains corresponding phenyl ethylenes.

[Problems that the Invention Intends to Solve]

Of the aforesaid prior-art methods, Methods 1) and 2) have problems, for example, in that their starting substances are expensive and not readily available and also in that both require a large number of process steps, some of which are troublesome process steps.

Methods 3) and 4) are examples that require a relatively small number of process steps. Even with Methods 3) and 4), however, the synthesis of their starting materials is hardly an easy process.

Since Method 4) requires a small number of process steps and yields the object substance at a high yield, it is promising as an industrial method. However, for implementing the process of obtaining substituted phenyl ethylene, Method a) cannot be considered to be an industrially advantageous method because the raw materials, that is, substituted phenyl ethyl alcohol and substituted phenyl ethyl halide, are expensive and hard to obtain. With a method that utilizes decomposition, as Methods b) and c), because the substituent phenoxy group or methoxy group is unstable, this method produces a large quantity of by-products, thus making the refining process difficult.

With respect to Method d), its raw material, a cinnamic acid derivative, is expensive, and the yield of the target substance is also low. Method e) also uses an expensive raw material and has a low yield, and, as such, it cannot be considered to be an industrially advantageous method. With Method f), 4-methoxy phenyl ethylene is produced at a high yield, but, since this method employs thermally unstable carbonyl sulfide as the oxidizing agent, it presents problems in cost and operation.

The objective of the present invention is to solve the problems of the aforesaid conventional methods. More specifically, the present invention intends to provide a method for producing 2-(substituted phenyl) propionic acid or alkyl ester thereof economically from inexpensive and readily available raw materials by means of simple operations.

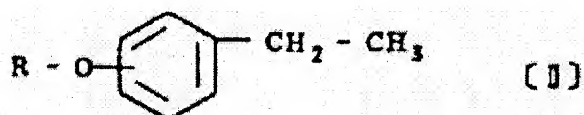
[Means of Solving the Problems]

The present inventors researched extensively to find a production method that is suitable for the industrial production of 2-(substituted phenyl) propionaldehyde represented by the aforesaid General Formula [I] and, as a result, achieved a new production method that uses substituted phenyl ethane as a raw material and that carries out a dehydrogenation process and a subsequent carbonylation process.

More specifically, the present invention pertains to a method for preparing 2-(substituted phenyl) propionaldehyde represented by

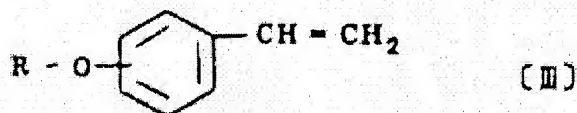
General Formula [I] presented in the foregoing, said method comprising the following steps (I) and (II):

(I) a step of dehydrogenating a substituted phenyl ethane represented by General Formula [II]:



(in which R represents a phenyl group or methyl group)

at 400 to 700°C in the presence of a dehydrogenation catalyst so as to prepare a substituted phenyl ethylene represented by General Formula [III]:



(in which R has the same meaning as defined in the foregoing) and

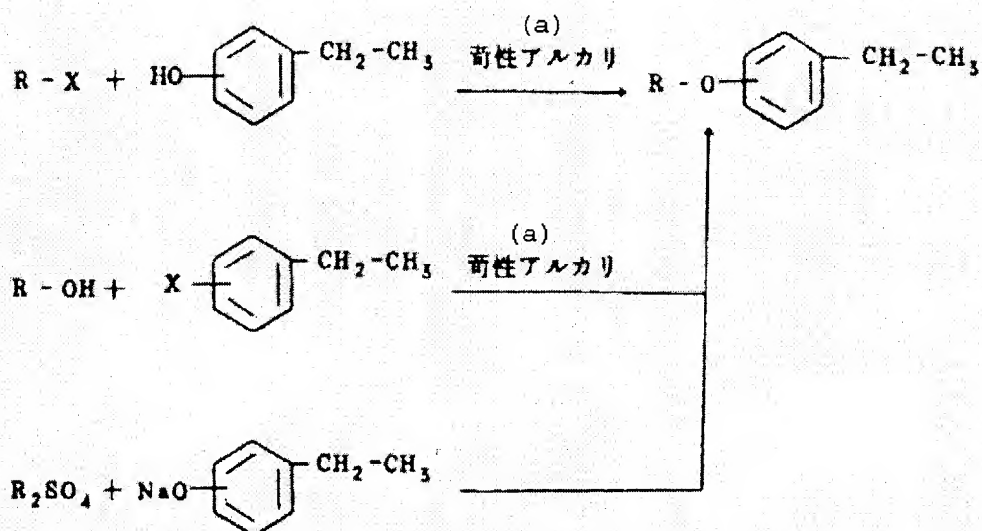
(II) a step of reacting the aforesaid substituted phenyl ethane with hydrogen and carbon monoxide in the presence of a hydroformylation catalyst so as to prepare the aforesaid 2-(substituted phenyl) propionaldehyde.

Therefore, according to the present invention, 2-(substituted phenyl) propionaldehyde can be obtained easily from substituted phenyl ethane, hydrogen, carbon monoxide, etc., which are raw materials that can be obtained inexpensively from the viewpoint of industrial production and in large quantities, through only two process steps.

The substituted phenyl ethane represented by the aforesaid General Formula [II], which is the starting material of the present

invention, is, specifically speaking, 3-phenoxy phenyl ethane, 4-phenoxy phenyl ethane, 2-phenoxy phenyl ethane, 3-methoxy phenyl ethane, 4-methoxy phenyl ethane, or 2-methoxy phenyl ethane. These substituted phenyl ethanes can be produced by any known conventional methods. As an example of the conventional synthesis methods, the method shown below is known, and the target substances can be synthesized easily from inexpensive materials.

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Key: a) caustic alkali.

(R= a phenyl group or a methyl group; X=Cl, Br, or I)

The following explains the method for implementing each process step in concrete terms.

The objective of Process Step I, which is the first-stage reaction in the method of the present invention, is to obtain substituted phenyl ethylene represented by General Formula [III]

presented in the foregoing by dehydrogenation of substituted phenyl ethane represented by General Formula [II] presented in the foregoing.

The substituent of the substituted phenyl ethane used in the present invention bonds with a phenyl group by means of an oxygen atom and is, consequently, susceptible to transition or detachment. In addition, with phenyl alkanes having this kind of substituent, their alkyl groups are, in general, prone to detach. Therefore, for Process Step I, it is essential to select a method that does not cause the transition or elimination of said substituent and ethyl group.

The present inventors researched extensively about this type of dehydrogenation reaction of substituted phenyl ethanes and, as a consequence, learned that the objective could be achieved by carrying out the reaction according to the method that produces alkenyl phenols by dehydrogenation of alkyl phenols. The method for dehydrogenating alkyl phenols is disclosed in JP-B-S49-041183, JP-B-S53-043491, JP-A-S54-055529, JP-A-S55-028958, JP-A-S57-203022, JP-A-S61-293942, etc., and, thus, it has been known. The process step (I) of the present invention is preferably implemented according to this type of dehydrogenation method of alkyl phenols. As the dehydrogenation catalyst, iron oxide, zinc oxide, magnesium oxide, chromium oxide, tin oxide, titanium oxide, barium oxide, etc., for example, can be used singly or as a mixture. The reaction temperature is usually 400 to 700 °C, preferably 450 to 650 °C. The feed rate of the raw material is usually selected from the range of 0.1 to 10 hr⁻¹ liquid hour space

velocity (LHSV) based on the catalyst. The reaction may be carried out either under atmospheric pressure, reduced pressure, or a pressurized condition, but it is practical to carry out the reaction under atmospheric pressure or thereabouts. The dehydrogenation reaction can be implemented advantageously with a lower partial pressure from the viewpoint of equilibrium, and it is usually carried out in the presence of a diluent. As the diluent, water, benzene, toluene, nitrogen gas, carbon dioxide gas, etc., are used. The amount of the diluent used here is 2 to 200 moles, preferably 3 to 100 moles, per 1 mole of the raw material. When a liquid substance, such as water, etc., is used as the diluent, the resulting product has the diluent mixed in it; therefore, part or all of it is eliminated as necessary.

The dehydrogenation reaction product obtained in this manner is a mixture that consists of unchanged substances and some amount of by-products besides the target substance, substituted phenyl ethylene, of the present step, and this mixture can be put to the subsequent process step (II) as it is or after the substituted phenyl ethylene is condensed or purified.

Process Step (II) is a step for obtaining 2-(substituted phenyl) propionaldehyde from the substituted phenyl ethylene obtained by the aforesaid process step (I). This method can be implemented according to a known hydroformylation method according to which an olefinic unsaturated compound is reacted with hydrogen and carbon monoxide in the presence of a hydroformylation catalyst.

Examples of the hydroformylation catalyst employed here include rhodium-based catalysts, platinum-tin-based catalysts, and cobalt-based catalysts, of which rhodium-based catalysts are especially preferable. There are many known rhodium-based catalysts that can be used for the hydroformylation reaction, and some concrete examples include hydride carbonyl tris (triphenyl phosphine) rhodium, /297 chloro carbonyl bis (triphenyl phosphine) rhodium, dichlorotetra carbonyl dirhodium, dodeca carbonyl tetrarhodium, chloro tris (triphenyl phosphine) rhodium, trichloro tris (triphenyl phosphine) rhodium, chlorobis (cyclo octene) rhodium, tetrakis triphenyl phosphine rhodium, dicarbonyl bis (triphenyl phosphine) rhodium, dichlorobis(tributyl phosphine) rhodium, dicarbonyl acetyl acetate rhodium, rhodium acetyl acetate, rhodium acetate, rhodium chloride, rhodium oxide, rhodium carbon, rhodium alumina, etc. The hydroformylation catalyst is used in the concentration range of 0.01 to 100 millimoles, preferably 0.1 to 10 millimoles, per 1 mole of the substituted penyl ethylene.

The hydroformylation catalysts cited in the foregoing can be used singly, but, the co-presence of a tertiary organic phosphorus compound in a quantity that is excess of the hydroformylation catalyst makes it possible to improve the yield of the target substance, stabilize the catalyst, and prevent the loss of catalyst activity during the reaction or the process for separating the product. There are a large number of this type of tertiary organic phosphorus compound, some

concrete examples of which include triphenyl phosphine, tritolyl phosphine, tributyl phosphine, triethyl phosphine, bis (1,2-diphenyl phosphino) ethane, triphenyl phosphite, etc. The amount of the organic phosphorus compound to be added in the case of using it in combination with the catalyst is usually from 1 to 100 moles, preferably 3 to 50 moles, per 1 mole of the hydroformylation catalyst used.

The hydrogen and carbon dioxide required for the reaction can be fed into a reactor separately or together as a gas mixture. The partial pressure ratio of hydrogen to carbon monoxide is preferably in the range from 1:2 to 10:1, ideally 1:1.

The reaction pressure is usually selected from the range of from atmospheric pressure to 350 kg/cm², preferably from 5 to 200 kg/cm². The reaction temperature is usually from 30 to 150 °C, preferably 50 to 120 °C. At a reaction temperature below 30 °C, a practical reaction speed cannot be attained, and, a reaction temperature exceeding 150 °C is not preferable because it causes such side reactions as polymerization, hydrogenation, etc. Generally speaking, it is sufficient to continue the reaction until the absorption of hydrogen and carbon monoxide becomes no longer observable, and a reaction time of 1 to 10 hours is usually sufficient.

The hydroformylation reaction of the substituted phenyl ethylene of the present invention generates not only the target substance, 2-(substituted phenyl) propionaldehyde, but also a small quantity of its

isomer, 3-(substituted phenyl) propionaldehyde, but these can be easily separated by a conventional distillation operation. Furthermore, the recovered catalyst can be reused for the carbonylation reaction.

[Effects of the Invention]

The method of the present invention uses inexpensive raw materials compared with conventional methods, and each of its process steps can be implemented with a simple operation without the need for handling complex intermediates or special chemical agents.

Since Process Step (I) of the present invention achieves dehydrogenation without the use of an oxidizing agent, it requires no special treatment and equipment from the standpoint of handling, thus rendering itself economical. In addition, when the substituted phenyl ethane obtained in Process Step (I) is used for the hydroformylation reaction of Process Step (II), the target substance can be obtained at a high yield, and, since the impurity content is small, refining is easier to implement; thus, the method of the present invention is advantageous for preparing the intermediate materials of pharmaceuticals, etc., which must have high purity.

As explained in the foregoing, the novel method of the present invention makes it possible to produce 2-(substituted phenyl) propionaldehyde with simple operations and at high yield as well as effectively and economically.

[Working Examples]

The present invention will hereinafter be described in further detail by the following working examples. It should, however, be borne in mind that the present invention is not limited to or by these examples.

Working Example 1

Process Step (I): Into a dehydrogenation reactor filled with 300 mL of a tin oxide catalyst, 3-phenoxy phenyl ethane, together with water in a quantity that was 10 times the moles of the 3-phenoxy phenyl ethane, was fed at an LHSV of 0.5 hr^{-1} , and a dehydrogenation reaction was carried out under atmospheric pressure at 580°C . The analysis of the obtained product by gas chromatography revealed that the conversion rate of the 3-phenoxy phenyl ethane was 61.3% and /298 the selectivity to 3-phenoxy phenyl ethylene was 96.3%. After water was separated from this reaction solution, the remaining solution was put to the next process step (II).

Process Step (II): 200 g of the aforesaid dehydrogenation reaction solution from which water had been eliminated and 0.7 g of hydride carbonyl tris (triphenyl phosphine) rhodium were charged into a 1,000 mL-capacity autoclave, and, while the reaction system was kept at 60 kg/cm^2 with an equimolar gas mixture of hydrogen and carbon monoxide, it was reacted at 70°C for 3 hours while it was being stirred.

After the autoclave was cooled to room temperature and the residual gas was released, the product was analyzed by gas chromatography according to the internal standard method, and the conversion rate of the 3-phenoxy phenyl ethylene was found to be 99.1%; the selectivity to 2-(3-phenoxy phenyl) propionaldehyde, 91.0%; and the selectivity to 3-(3-phenoxy phenyl) propionaldehyde, 4.3%.

The reaction product was distilled under reduced pressure, thereby obtaining 2-(3-phenoxy phenyl) propionaldehyde, and its structure was examined by NMR.

NMR (TMS, CDCl_3) δ (ppm): 1.41 (d, 3H), 3.57 (q, 1H), 6.85-7.40 (m, 6H), 9.66 (d, 1H)

Working Example 2

Process Step (I): Into the same dehydrogenation reactor as the one used in Working Example 1, 4-phenoxy phenyl ethane, together with benzene in a quantity that was 10 times the moles of the 4-phenoxy phenyl ethane, was fed at an LHSV of 0.5 hr^{-1} , and a dehydrogenation reaction was carried out under atmospheric pressure at 530°C . The resulting conversion rate of the 4-phenoxy phenyl ethane was 20.5%, and the selectivity to 4-phenoxy phenyl ethylene was 95.3%. After benzene was distilled away from this reaction solution under reduced pressure, the remaining solution was put to the next process step (II).

Process Step (II): A hydroformylation reaction was carried out in the same manner as in Working Example 1, except that 400 g of the aforesaid dehydrogenation reaction solution from which benzene had

been eliminated was used in this case. The resulting conversion rate of the 4-phenoxy phenyl ethylene was 93.8%; the selectivity to 2-(4-phenoxy phenyl) propionaldehyde, 90.2%; and the selectivity to 3-(4-phenoxy phenyl) propionaldehyde, 6.3%.

Working Example 3

Process Step (I): A dehydrogenation reaction was carried out in the same manner as in Working Example 1, except that 4-methoxy phenyl ethane was used in place of 3-phenoxy phenyl ethane, the LHSV was set to 0.3 hr^{-1} , and the reaction temperature was set to 490°C . The resulting conversion rate of the 4-methoxy phenyl ethane was 18.8%, and the selectivity to 4-methoxy phenyl ethylene was 92.0%. After water was separated from this reaction solution, the remaining solution was put to the next process step (II).

Process Step (II): A hydroformylation reaction was carried out in the same manner as in Working Example 1, except that 400 g of the aforesaid dehydrogenation reaction solution from which water was eliminated was used in this case. The resulting conversion rate of the 4-methoxy phenyl ethylene was 91.9%, the selectivity to 2-(4-methoxy phenyl) propionaldehyde was 88.7%, and the selectivity to 3-(4-methoxy phenyl) propionaldehyde was 9.0%.

Working Example 4

Process Step (I): A dehydrogenation reaction was carried out in the same manner as in Working Example 2, except that 3-methoxy phenyl ethane was used in place of 4-phenoxy phenyl ethane, the LHSV was set

to 0.3 hr^{-1} , and the reaction temperature was set to 560°C . The resulting conversion rate of the 3-methoxy phenyl ethane was 58.8%, and the yield of 3-methoxy phenyl ethylene to the converted 3-methoxy phenyl ethane was 93.9%. This reaction solution was distilled, thereby obtaining a fraction comprised of 68% of 3-methoxy phenyl ethylene and 32% of 3-methoxy phenyl ethane.

Process Step (II): A hydroformylation reaction was carried out in the same manner as in Working Example 1, except that 200 g of the aforesaid fraction was used in this case. The resulting conversion rate of the 3-methoxy phenyl ethylene was 98.7%; the selectivity to 2-(3-methoxy phenyl) propionaldehyde, 90.5%; and the selectivity to 3-(3-methoxy phenyl) propionaldehyde, 6.1%.

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CY=JA DATE=19881128 KIND=A
PN=63-290842

METHOD FOR PREPARING 2-(SUBSTITUTED PHENYL) PROPIONIC ACID
OR ALKYL ESTER THEREOF
[2-(Chikan Feniru) Puropionsan Mataha Sono Arukiru Esteru No Seizoho]

Eiji Takahashi, et al.

UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C. August 2004

Translated by: FLS, Inc.

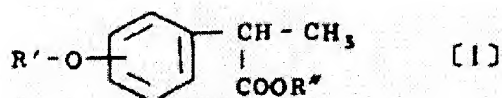
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DOMESTIC CLASSIFICATION	(52):
PRIORITY COUNTRY	(33):
PRIORITY NUMBER	(31):
PRIORITY DATE	(32):
INVENTORS	(72): TAKAHASHI, EIJI; OZAKI, KAZUO; YAMADA, TAKAO
APPLICANT	(71): MARUZEN PETROCHEMICAL CO., LTD.
TITLE	(54): METHOD FOR PREPARING 2- (SUBSTITUTED PHENYL) PROPIONIC ACID OR ALKYL ESTER THEREOF
FOREIGN TITLE	[54A]: 2-(Chikan Feniru) Puropionsan Mataha Sono Arukiru Esteru No Seizoho

1. Title

METHOD FOR PREPARING 2-(SUBSTITUTED PHENYL) PROPIONIC ACID OR ALKYL
ESTER THEREOF

2. Claims

A method for preparing 2-(substituted phenyl) propionic acid
represented by General Formula [I]:

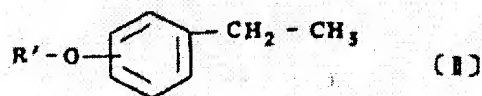


(in which R' is a phenyl group or a methyl group and R'' is a hydrogen
atom or a lower alkyl group)

or an alkyl ester thereof,

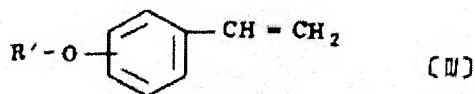
said method comprising the following process steps I and II:

(I) a step of dehydrogenating a substituted phenyl ethane represented
by General Formula [II]:



(in which R' has the same meaning as defined in the foregoing)

at 400 to 700 °C in the presence of a dehydrogenation catalyst so as
to prepare a substituted phenyl ethylene represented by General
Formula [III]:



(in which R' has the same meaning as defined in the foregoing) and

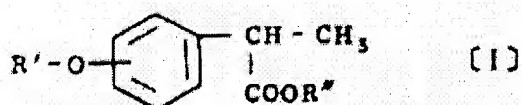
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(II) a step of reacting the aforesaid substituted phenyl ethane with carbon monoxide and with water or a lower alcohol in the presence of a palladium-based catalyst so as to prepare the aforesaid 2-(substituted phenyl) propionic acid or an alkyl ester thereof.

3. Detailed Description of the Invention

[Industrial Field of Application]

The present invention pertains to a novel method for economically preparing 2-(substituted phenyl) propionic acid represented by General Formula [I]:



(in which R' is a phenyl group or a methyl group and R'' is a hydrogen atom or a lower alkyl group) and an alkyl ester thereof. /326

Many of the 2-(substituted phenyl) propionic acids represented by General formula [I] and their alkyl esters are useful as pharmaceuticals or intermediates thereof. For example, 2-(3-phenoxy phenyl) propionic acid that is obtained according to the method of the present invention has anti-inflammatory, analgesic, and antipyretic effects and is known by its common name "fenoprofen."

[Prior Art]

Numerous methods have been proposed for the production of 2-(substituted phenyl) propionic acids represented by General Formula [I] and derivatives thereof, and the following presents some representative processes.

1) A method that reduces an acetophenone derivative having a substituent at the aromatic nucleus so as to convert it into 1-(substituted phenyl) ethyl alcohol and subsequently carries out halogen substitution, cyanidation, and hydrolysis (see U.S. Patent No. 3,600,437 and JP-A-S58-077841)

2) A method that reacts a phenyl acetic acid ester having a substituent at the aromatic nucleus with dialkyl carbonate, thereby converting it into a corresponding malonic acid diester, which is methylated with methyl iodide, subsequently hydrolyzed, and then decarbonated (see JP-B-S51-045586)

3) A method that oxidizes 2-(substituted phenyl) propionaldehyde or 3-methyl-3-(substituted phenyl) pyruvic acid (see JP-A-S51-016636, JP-A-S53-012835, and JP-A-S54-039043)

The aforesaid propionaldehyde derivative and pyruvic acid derivative can be synthesized, for example, by treating a 3-methyl-3-(substituted phenyl) glycidic acid ester, which is obtained by the reaction of an acetophenone derivative having a substituent at the aromatic nucleus with a monochloro acetic acid ester, with a mineral acid under a water-containing condition (see JP-B-S56-020239 and JP-B-S59-041976.)

4) A method that carbonylates a substituted phenyl ethylene by reacting it with carbon monoxide and with a lower alcohol or water in the presence of a palladium-based catalyst (see JP-B-60-045171).

The aforesaid phenyl ethylene corresponds to the phenoxy phenyl ethylene and methoxy phenyl ethylene in the present invention. The most widely practiced method for producing this type of substituted phenyl ethylene having a phenoxy group or methoxy group at the aromatic nucleus as the substituent is a) dehydration or dehydrohalogenation of a corresponding substituted phenyl ethyl alcohol or substituted phenyl ethyl halide. For example, a method for producing 3-phenoxy phenyl ethylene by dehydration of 1-(3-phenoxy phenyl) ethyl alcohol is known (see JP-A-S53-018533). Other known methods include b) a method that employs decomposition of diaryl ethanes (see "Ind. Eng. Chem. Prod. Res. Develop.," 3(1), 16, 1964); c) a method that decomposes anisole having an alkyl group that has 3 or more carbon atoms, thereby obtaining 3-methoxy phenyl ethylene (see U.S. Patent No. 2,698,868); d) a method that decarbonates methoxy cinnamic acid (see "J. Applied Chem." 1, 95, 1951); e) a method that heats an acetophenone derivative having a substituent at the aromatic nucleus together with aluminum alkoxide (see JP-A-S49-086332); f) a method that obtains 4-methoxy phenyl ethylene by oxidative dehydrogenation of 4-methoxy phenyl ethane, using carbonyl sulfide as the oxidizing agent (see U.S. Patent NO. 3,875,252); and so forth. However, there is no method that dehydrogenates phenyl ethanes having phenoxy groups or methoxy groups without the use of an oxidizing agent and thereby obtains corresponding phenyl ethylenes.

[Problems that the Invention Intends to Solve]

Of the aforesaid prior-art methods, Methods 1) and 2) have problems, for example, in that their starting substances are expensive and not readily available and also in that both require a large number of process steps, some of which are troublesome process steps.

Methods 3) and 4) are examples that require a relatively small number of process steps. Even with Method 3), however, the synthesis of their starting materials is hardly an easy process.

Since Method 4) requires only a small number of process steps and its yield of the target substance is also high, this method is promising as an industrial method. However, with respect to the methods for obtaining a substituted phenyl ethylene, Method a) cannot be considered to be an industrially advantageous method because the raw materials, that is, substituted phenyl ethyl alcohol and substituted phenyl ethyl halide, are expensive and hard to obtain. /327 With a method that utilizes decomposition, as Methods b) and c), because the substituent phenoxy group or methoxy group is unstable, this method produces a large quantity of by-products, thus making the refining process difficult. With respect to Method d), its raw material, a cinnamic acid derivative, is expensive, and the yield of the target substance is also low. Method e) also uses an expensive raw material and has a low yield, and, as such, it cannot be considered to be an industrially advantageous method. With Method f), 4-methoxy phenyl ethylene is produced at a high yield, but, since this method

employs thermally unstable carbonyl sulfide as the oxidizing agent, it presents problems in cost and operation.

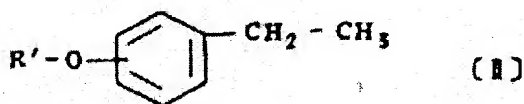
The objective of the present invention is to solve the problems of the aforesaid conventional methods. More specifically, the present invention intends to provide a method for producing 2-(substituted phenyl) propionic acid or an alkyl ester thereof economically from inexpensive and readily available raw materials by means of simple operations.

[Means of Solving the Problems]

The present inventors researched extensively to find a production method that is suitable for the industrial production of 2-(substituted phenyl) propionic acid represented by the aforesaid General Formula [I] and an alkyl ester thereof, and, as a result, achieved a new production method that uses substituted phenyl ethane as a raw material and that carries out a dehydrogenation process and subsequently a carbonylation process.

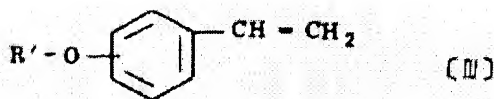
More specifically, the present invention pertains to a method for preparing 2-(substituted phenyl) propionic acid represented by General Formula [I] presented in the foregoing or an alkyl ester thereof, said method comprising the following steps I and II:

(I) a step of dehydrogenating a substituted phenyl ethane represented by General Formula [II]:



(in which R' represents a phenyl group or a methyl group)

at 400 to 700 °C in the presence of a dehydrogenation catalyst so as to prepare a substituted phenyl ethylene represented by General Formula [III]:



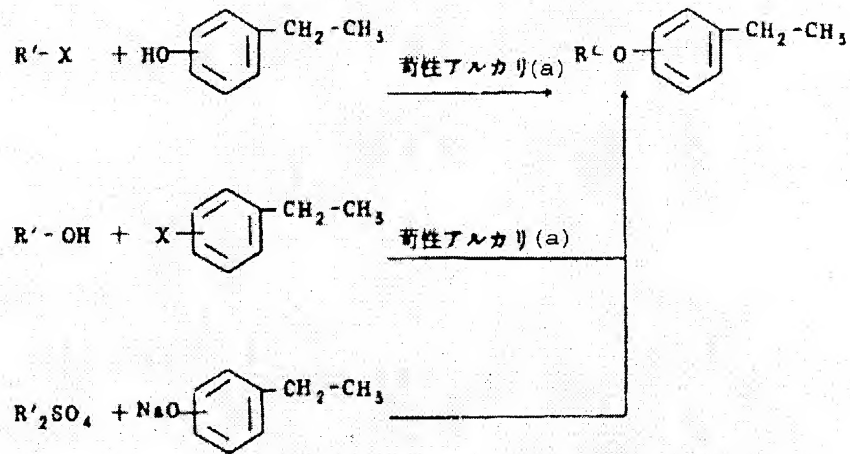
(in which R' has the same meaning as defined in the foregoing) and

(II) a step of reacting the aforesaid substituted phenyl ethane with carbon monoxide and with water or a lower alcohol in the presence of a palladium-based catalyst so as to prepare the aforesaid 2-(substituted phenyl) propionic acid or an alkyl ester thereof.

Therefore, according to the present invention, 2-(substituted phenyl) propionic acid or an alkyl ester thereof can be obtained easily from substituted phenyl ethane, carbon monoxide, and water or a lower alcohol, which are raw materials that can be obtained inexpensively from the viewpoint of industrial production and in large quantities, through only two process steps.

The substituted phenyl ethane represented by the aforesaid General Formula [II], which is the starting material of the present invention, is, specifically speaking, 3-phenoxy phenyl ethane, 4-phenoxy phenyl ethane, 2-phenoxy phenyl ethane, 3-methoxy phenyl ethane, 4-methoxy phenyl ethane, or 2-methoxy phenyl ethane. These substituted phenyl ethanes can be produced by any known conventional methods. As an example of the conventional synthesis methods, the

method shown below is known, and the target substances can be synthesized easily from inexpensive materials.



Key: a) caustic alkali.

(R' = a phenyl group or a methyl group; X = Cl, Br, or I)

The following explains the method for implementing each process step in concrete terms.

The objective of Process Step I, which is the first-stage reaction in the method of the present invention, is to obtain a substituted phenyl ethylene represented by General Formula [III] presented in the foregoing by dehydrogenation of substituted phenyl ethane represented by General Formula [II] presented in the foregoing.

The substituent of the substituted phenyl ethane used in the present invention bonds with a phenyl group by means of an oxygen atom and is, consequently, susceptible to transition or detachment. In addition, with phenyl alkanes having this kind of substituent, their alkyl groups are, in general, prone to detach. Therefore, for Process

Step I, it is essential to select a method that does not cause the transition or elimination of said substituent and ethyl group.

The present inventors researched extensively about this type of dehydrogenation reaction of substituted phenyl ethanes and, as a consequence, learned that the objective could be achieved by carrying out the reaction according to the method that produces alkenyl phenols by dehydrogenation of alkyl phenols. The method for dehydrogenating alkyl phenols is disclosed in JP-B-S49-041183, JP-B-S53-043491, JP-A-S54-055529, JP-A-S55-028958, JP-A-S57-203022, JP-A-S61-293942, etc., and, thus, it has been known. That is, Process Step I of the present invention is preferably implemented according to this type of dehydrogenation method of alkyl phenols. As the dehydrogenation catalyst, iron oxide, zinc oxide, magnesium oxide, chromium oxide, tin oxide, titanium oxide, barium oxide, etc., for example, can be used singly or as a mixture. The reaction temperature is usually from 400 to 700 °C, preferably from 450 to 650 °C. The feed rate of the raw material is usually selected from the range of 0.1 to 10 hr⁻¹ liquid hour space velocity (LHSV) based on the catalyst. The reaction may be carried out either under atmospheric pressure, reduced pressure, or a pressurized condition, but it is practical to carry out the reaction under atmospheric pressure or thereabouts. The dehydrogenation reaction can be implemented advantageously with a lower partial pressure from the viewpoint of equilibrium, and it is usually carried out in the presence of a diluent. As the diluent, water, benzene,

toluene, nitrogen gas, carbon dioxide gas, etc., are used. The amount of the diluent used here is 2 to 200 moles, preferably 3 to 100 moles, per 1 mole of the raw material. When a liquid substance, such as water, etc., is used as the diluent, the resulting product has the diluent mixed in it; therefore, part or all of it is eliminated as necessary.

The dehydrogenation reaction product obtained in this manner is a mixture that consists of unchanged substances and some amount of by-products besides the target substance, that is, substituted phenyl ethylene, of the present step, and this mixture can be put to the subsequent process step II as it is or after the substituted phenyl ethylene is condensed or purified.

Process Step II is a step for obtaining 2-(substituted phenyl) propionic acid or an alkyl ester thereof from the substituted phenyl ethylene obtained by the aforesaid process step I. This method can be implemented according to a known carbonylation method according to which an olefinic unsaturated compound is reacted with carbon monoxide and with water or a lower alcohol in the presence of a palladium-based catalyst. The use of water here yields a 2-(substituted phenyl) propionic acid, while the use of a lower alcohol yields an alkyl ester corresponding to it.

As the palladium-based catalyst employed here, palladium complexes are suitable, and palladium complexes having a palladium atomic value of from 0 to 2 and having, as the ligand, a halogen atom, trivalent phosphorous compound, π -allyl group, amine, nitrile, oxime, /32

olefin, carbon dioxide, etc., are effective. Concrete examples include bistriphenyl phosphine dichloro palladium, bis(tributyl phosphine) dichloro palladium, bis(cyclohexyl phosphine) dichloro palladium, π -allyl triphenyl phosphine chloro palladium, triphenyl phosphine piperidine dichloro palladium, bis(benzonitrile) dichloro palladium, bis(cyclohexyl oxime) dichloro palladium, 1,5,9-cyclo dodeca triene-dichloro palladium, bistriphenyl phosphine dicarbonyl palladium, bistriphenyl phosphine palladium acetate, tetrakis triphenyl phosphine palladium, etc. These need not be isolated in the form of palladium complexes for the use as the catalyst of the present invention, and it is possible to use compounds that can form the aforesaid complexes in the reaction system. More specifically, the present invention can employ a method that brings both a palladium salt, such as palladium oxide, palladium sulfate, palladium chloride, etc., and a compound that can become a ligand, such as phosphine, nitrile, an allyl compound, amine, oxime, olefin, carbon dioxide, etc., into the reaction system simultaneously.

Some examples of the phosphine here include triphenyl phosphine, tritolyl phosphine, tributyl phosphine, triethyl phosphine, etc. Some examples of the nitrile include benzonitrile, propionitrile, etc. Some examples of the allyl compound include allyl chloride, allyl alcohol, etc. Some examples of the amine include benzyl amine, pyridine, etc. Some examples of the oxime include cyclohexyl oxime, acetoxime, etc. Some examples of the olefin include 1,5-cyclo octadiene, 1,5,9-cyclo

dodeca triene, etc. The addition amount of these compounds that can become ligands is 0.8 to 10 moles, preferably 1 to 4 moles, per 1 gram atom of palladium.

The quantity of palladium used in the reaction is 0.0001 to 0.5 gram atom, preferably 0.001 to 0.1 gram atom, per 1 mole of the substituted phenyl ethylene. The aforesaid type of palladium-based catalyst can exhibit its activity without the use of a catalyst aid, but, for the purpose of further improving the reaction speed, hydrogen chloride, boron trifluoride, iodine, etc., may be added as catalyst aids in a trace amount.

The lower alcohol used for the method of the present invention is not limited in any specific way, and some examples of it include methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, sec-butanol, etc. Alcohol and water are reaction materials and also function as solvents, and they are used in a quantity of 0.5 to 50 parts by weight, preferably 1 to 20 parts by weight, per 1 part of the substituted phenyl ethylene.

The carbonylation reaction is carried out at a reaction temperature of 40 to 200 °C, preferably 60 to 150 °C, under a pressure of 30 to 400 kg/cm², preferably 50 to 300 kg/cm², created by carbon monoxide.

Generally speaking, it is sufficient to continue the reaction until the absorption of carbon monoxide becomes no longer observable,

and a reaction time of 1 to 10 hours can produce the target substance at a satisfactory yield.

The carbonylation reaction of the substituted phenyl ethylene of the present process generates not only the target substances, that is, 2-(substituted phenyl) propionic acid and an alkyl ester thereof, but also its isomer 3-(substituted phenyl) propionic acid and an alkyl ester thereof in small quantities, but these can be easily separated by a conventional distillation operation. Furthermore, the recovered catalyst can be reused for the carbonylation reaction.

[Effects of the Invention]

The method of the present invention uses inexpensive raw materials compared with conventional methods, and each of its process steps can be implemented with a simple operation without the need for handling complex intermediates or special chemical agents.

Since Process Step I of the present invention achieves dehydrogenation without the use of an oxidizing agent, it requires no special treatment and equipment from the standpoint of handling, thus rendering itself economical. In addition, when the substituted phenyl ethane obtained in Process Step I is used for the carbonylation reaction of Process Step II, the target substance can be obtained at a high yield, and, since the impurity content is small, refining is easier to implement; thus, the method of the present invention is advantageous for preparing pharmaceuticals or intermediate materials /330 thereof, which must have high purity.

As explained in the foregoing, the novel method of the present invention makes it possible to produce 2-(substituted phenyl) propionic acid or an alkyl ester thereof with simple operations and at a high yield as well as effectively and economically.

[Working Examples]

The present invention will hereinafter be described in further detail by the following working examples. It should, however, be borne in mind that the present invention is not limited to or by these examples.

Working Example 1

Process Step I: Into a dehydrogenation reactor filled with 300 mL of a tin oxide catalyst, 3-phenoxy phenyl ethane, together with water in a quantity that was 10 times the moles of the 3-phenoxy phenyl ethane, was fed at an LHSV of 0.5 hr^{-1} , and a dehydrogenation reaction was carried out under atmospheric pressure at 580°C . The analysis of the obtained product by gas chromatography revealed that the conversion rate of the 3-phenoxy phenyl ethane was 61.3% and the selectivity to 3-phenoxy phenyl ethylene was 96.3%. After water was separated from this reaction solution, the remaining solution was put to the next process step II.

Process Step II: 100 g of the aforesaid dehydrogenation reaction solution from which water had been eliminated, 250 g of isopropyl alcohol, 1.0 g of bistriphenyl phosphine dichloro palladium, 0.5 g of triphenyl phosphine, and 0.5 g of 35% hydrochloric acid were charged

into a 1,000 mL-capacity autoclave, and, while the autoclave was pressurized to 120 kg/cm² with carbon monoxide, the reaction system was reacted at 110 °C for 3 hours.

After the autoclave was cooled to room temperature and the residual gas was released, the product was analyzed by gas chromatography according to the internal standard method, and the conversion rate of the 3-phenoxy phenyl ethylene was found to be 99.8%, the selectivity to 2-(3-phenoxy phenyl) propionic acid isopropyl ester was found to be 93.2%, and the selectivity to 3-(3-phenoxy phenyl) propionic acid isopropyl ester was found to be 6.4%.

The aforesaid reaction solution was distilled under reduced pressure, thereby obtaining 2-(3-phenoxy phenyl) propionic acid isopropyl ester, and its structure was examined by NMR.

NMR (TMS, CDCl₃) δ (ppm): 1.13-1.23 (dd, 6H), 1.46 (d, 3H), 3.66 (q, 1H), 5.00 (m, 1H), 6.90-7.39 (m, 9H)

Working Example 2

Process Step I: Into the same dehydrogenation reactor as the one used in Working Example 1, 4-phenoxy phenyl ethane, together with benzene in a quantity that was 10 times the moles of the 4-phenoxy phenyl ethane, was fed at an LHSV of 0.5 hr⁻¹, and a dehydrogenation reaction was carried out under atmospheric pressure at 530 °C. The resulting conversion rate of the 4-phenoxy phenyl ethane was 20.5%, and the selectivity to 4-phenoxy phenyl ethylene was 95.3%. After

benzene was distilled away from this reaction solution under reduced pressure, the remaining solution was put to the next process step II.

Process Step II: 100 g of the aforesaid dehydrogenation reaction solution from which benzene had been eliminated, 250 g of sec-butanol, 1.0 g of bistriphenyl phosphine dichloro palladium, and 0.2 g of a 30% boron trifluoride ether complex were charged into a 1,000 mL-capacity autoclave, and, while the autoclave was pressurized to 80 kg/cm² with carbon monoxide, the reaction system was reacted at 70 °C until the absorption of carbon dioxide became no longer observable.

The analyses of the obtained reaction solution revealed that the resulting conversion rate of the 4-phenoxy phenyl ethylene was 99.8%, the selectivity to 2-(4-phenoxy phenyl) propionic acid sec-butyl ester was 92.6%, and the selectivity to 3-(4-phenoxy phenyl) propionic acid sec-butyl ester was 7.0%.

Working Example 3

Process Step (I): Into the same dehydrogenation reactor as the one used in Working Example 1, 3-phenoxy phenyl ethane, together with benzene in a quantity that was 10 times the moles of the 3-phenoxy phenyl ethane, was fed at an LHSV of 0.3 hr⁻¹, and a dehydrogenation reaction was carried out under atmospheric pressure at 560 °C. The resulting conversion rate of the 3-phenoxy phenyl ethane was 57.1%, and the selectivity to 3-phenoxy phenyl ethylene was 94.1%.

Process Step II: 50 g of the aforesaid dehydrogenation reaction solution containing benzene, 30 mL of a 10% aqueous solution of

hydrochloric acid, and 0.5 g of bistriphenyl phosphine dichloro palladium were charged into a 200 mL-capacity autoclave, and, while the autoclave was pressurized to 200 kg/cm² with carbon monoxide, the reaction system was reacted at 120 °C until the absorption of carbon dioxide became no longer observable. After the reaction system was /331 cooled to room temperature, the reaction solution was mixed with sodium carbonate to implement alkali extraction, thereby separating a benzene layer, after which the extracted solution was made acidic with hydrochloric acid and extracted with ether. The ether layer was washed with water and dried over magnesium sulfate, and ether was distilled away, thereby obtaining 5.1 g of 2-(3-phenoxy phenyl) propionic acid.

Working Example 4

Process Step (I): Into the same dehydrogenation reactor as the one used in Working Example 1, 4-methoxy phenyl ethane, together with water in a quantity that was 10 times the moles of the 4-methoxy phenyl ethane, was fed at an LHSV of 0.3 hr⁻¹, and a dehydrogenation reaction was carried out under atmospheric pressure at 490 °C. The resulting conversion rate of the 4-methoxy phenyl ethane was 18.8%, and the selectivity to 4-methoxy phenyl ethylene was 92.0%. After water was separated from this reaction solution, the remaining solution was put to the next process step II.

Process Step II: 100 g of the aforesaid dehydrogenation reaction solution from which water had been eliminated, 250 g of sec-butanol, 1.0 g of bistriphenyl phosphine dichloro palladium, 0.5 g of triphenyl

phosphine, and 0.5 g of 35% hydrochloric acid were charged into a 1,000 mL-capacity autoclave, and, while the autoclave was pressurized to 120 kg/cm² with carbon monoxide, the reaction system was reacted at 110 °C until the absorption of carbon monoxide became no longer observable.

The analyses of the obtained reaction solution revealed that the resulting conversion rate of the 4-methoxy phenyl ethylene was 99.0%, the selectivity to 2-(4-methoxy phenyl) propionic acid sec-butyl ester was 93.0%, and the selectivity to 3-(4-methoxy phenyl) propionic acid sec-butyl ester was 5.9%.

Working Example 5

Process Step (I): Into the same dehydrogenation reactor as the one used in Working Example 1, 3-methoxy phenyl ethane, together with benzene in a quantity that was 10 times the moles of the 3-methoxy phenyl ethane, was fed at an LHSV of 0.3 hr⁻¹, and a dehydrogenation reaction was carried out under atmospheric pressure at 560 °C. The resulting conversion rate of the 3-methoxy phenyl ethane was 58.8%, and the yield of 3-methoxy phenyl ethylene to the converted 3-methoxy phenyl ethane was 93.9%. This reaction solution was distilled, thereby obtaining a fraction comprised of 68% of 3-methoxy phenyl ethylene and 32% of 3-methoxy phenyl ethane.

Process Step II: A reaction was carried out in the same manner as in Process Step II of Working Example 1, except that 100 g of the aforesaid fraction was used in this case. The resulting conversion

rate of the 3-methoxy phenyl ethylene was 99.8%, the selectivity to 2-(3-methoxy phenyl) propionic acid isopropyl ester was 93.2%, and the selectivity to 3-(3-methoxy phenyl) propionic acid isopropyl ester was 6.3%.

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PN=63-290842

METHOD FOR PREPARING 2-(SUBSTITUTED PHENYL) PROPIONIC ACID
OR ALKYL ESTER THEREOF
[2-(Chikan Feniru) Puropionsan Mataha Sono Arukiru Esteru No Seizoho]

Eiji Takahashi, et al.

UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C. August 2004

Translated by: FLS, Inc.

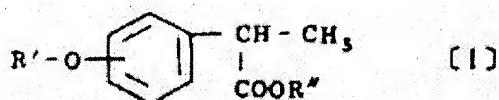
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FOREIGN TITLE	[54A]: 2-(Chikan Feniru) Puropionsan Mataha Sono Arukiru Esteru No Seizoho

1. Title

METHOD FOR PREPARING 2-(SUBSTITUTED PHENYL) PROPIONIC ACID OR ALKYL
ESTER THEREOF

2. Claims

A method for preparing 2-(substituted phenyl) propionic acid
represented by General Formula [I]:

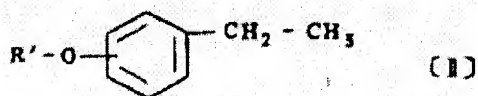


(in which R' is a phenyl group or a methyl group and R'' is a hydrogen
atom or a lower alkyl group)

or an alkyl ester thereof,

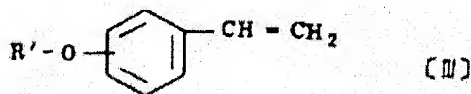
said method comprising the following process steps I and II:

(I) a step of dehydrogenating a substituted phenyl ethane represented
by General Formula [II]:



(in which R' has the same meaning as defined in the foregoing)

at 400 to 700 °C in the presence of a dehydrogenation catalyst so as
to prepare a substituted phenyl ethylene represented by General
Formula [III]:



(in which R' has the same meaning as defined in the foregoing) and

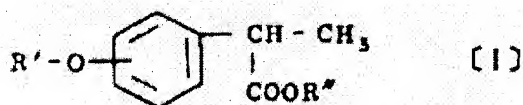
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(II) a step of reacting the aforesaid substituted phenyl ethane with carbon monoxide and with water or a lower alcohol in the presence of a palladium-based catalyst so as to prepare the aforesaid 2-(substituted phenyl) propionic acid or an alkyl ester thereof.

3. Detailed Description of the Invention

[Industrial Field of Application]

The present invention pertains to a novel method for economically preparing 2-(substituted phenyl) propionic acid represented by General Formula [I]:



(in which R' is a phenyl group or a methyl group and R'' is a hydrogen atom or a lower alkyl group) and an alkyl ester thereof. /326

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Many of the 2-(substituted phenyl) propionic acids represented by General formula [I] and their alkyl esters are useful as pharmaceuticals or intermediates thereof. For example, 2-(3-phenoxy phenyl) propionic acid that is obtained according to the method of the present invention has anti-inflammatory, analgesic, and antipyretic effects and is known by its common name "fenoprofen."

[Prior Art]

Numerous methods have been proposed for the production of 2-(substituted phenyl) propionic acids represented by General Formula [I] and derivatives thereof, and the following presents some representative processes.

1) A method that reduces an acetophenone derivative having a substituent at the aromatic nucleus so as to convert it into 1-(substituted phenyl) ethyl alcohol and subsequently carries out halogen substitution, cyanidation, and hydrolysis (see U.S. Patent No. 3,600,437 and JP-A-S58-077841)

2) A method that reacts a phenyl acetic acid ester having a substituent at the aromatic nucleus with dialkyl carbonate, thereby converting it into a corresponding malonic acid diester, which is methylated with methyl iodide, subsequently hydrolyzed, and then decarbonated (see JP-B-S51-045586)

3) A method that oxidizes 2-(substituted phenyl) propionaldehyde or 3-methyl-3-(substituted phenyl) pyruvic acid (see JP-A-S51-016636, JP-A-S53-012835, and JP-A-S54-039043)

The aforesaid propionaldehyde derivative and pyruvic acid derivative can be synthesized, for example, by treating a 3-methyl-3-(substituted phenyl) glycidic acid ester, which is obtained by the reaction of an acetophenone derivative having a substituent at the aromatic nucleus with a monochloro acetic acid ester, with a mineral acid under a water-containing condition (see JP-B-S56-020239 and JP-B-S59-041976.)

4) A method that carbonylates a substituted phenyl ethylene by reacting it with carbon monoxide and with a lower alcohol or water in the presence of a palladium-based catalyst (see JP-B-60-045171).

The aforesaid phenyl ethylene corresponds to the phenoxy phenyl ethylene and methoxy phenyl ethylene in the present invention. The most widely practiced method for producing this type of substituted phenyl ethylene having a phenoxy group or methoxy group at the aromatic nucleus as the substituent is a) dehydration or dehydrohalogenation of a corresponding substituted phenyl ethyl alcohol or substituted phenyl ethyl halide. For example, a method for producing 3-phenoxy phenyl ethylene by dehydration of 1-(3-phenoxy phenyl) ethyl alcohol is known (see JP-A-S53-018533). Other known methods include b) a method that employs decomposition of diaryl ethanes (see "Ind. Eng. Chem. Prod. Res. Develop.," 3(1), 16, 1964); c) a method that decomposes anisole having an alkyl group that has 3 or more carbon atoms, thereby obtaining 3-methoxy phenyl ethylene (see U.S. Patent No. 2,698,868); d) a method that decarbonates methoxy cinnamic acid (see "J. Applied Chem." 1, 95, 1951); e) a method that heats an acetophenone derivative having a substituent at the aromatic nucleus together with aluminum alkoxide (see JP-A-S49-086332); f) a method that obtains 4-methoxy phenyl ethylene by oxidative dehydrogenation of 4-methoxy phenyl ethane, using carbonyl sulfide as the oxidizing agent (see U.S. Patent NO. 3,875,252); and so forth. However, there is no method that dehydrogenates phenyl ethanes having phenoxy groups or methoxy groups without the use of an oxidizing agent and thereby obtains corresponding phenyl ethylenes.

[Problems that the Invention Intends to Solve]

Of the aforesaid prior-art methods, Methods 1) and 2) have problems, for example, in that their starting substances are expensive and not readily available and also in that both require a large number of process steps, some of which are troublesome process steps.

Methods 3) and 4) are examples that require a relatively small number of process steps. Even with Method 3), however, the synthesis of their starting materials is hardly an easy process.

Since Method 4) requires only a small number of process steps and its yield of the target substance is also high, this method is promising as an industrial method. However, with respect to the methods for obtaining a substituted phenyl ethylene, Method a) cannot be considered to be an industrially advantageous method because the raw materials, that is, substituted phenyl ethyl alcohol and substituted phenyl ethyl halide, are expensive and hard to obtain. /327 With a method that utilizes decomposition, as Methods b) and c), because the substituent phenoxy group or methoxy group is unstable, this method produces a large quantity of by-products, thus making the refining process difficult. With respect to Method d), its raw material, a cinnamic acid derivative, is expensive, and the yield of the target substance is also low. Method e) also uses an expensive raw material and has a low yield, and, as such, it cannot be considered to be an industrially advantageous method. With Method f), 4-methoxy phenyl ethylene is produced at a high yield, but, since this method

employs thermally unstable carbonyl sulfide as the oxidizing agent, it presents problems in cost and operation.

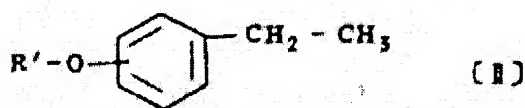
The objective of the present invention is to solve the problems of the aforesaid conventional methods. More specifically, the present invention intends to provide a method for producing 2-(substituted phenyl) propionic acid or an alkyl ester thereof economically from inexpensive and readily available raw materials by means of simple operations.

[Means of Solving the Problems]

The present inventors researched extensively to find a production method that is suitable for the industrial production of 2-(substituted phenyl) propionic acid represented by the aforesaid General Formula [I] and an alkyl ester thereof, and, as a result, achieved a new production method that uses substituted phenyl ethane as a raw material and that carries out a dehydrogenation process and subsequently a carbonylation process.

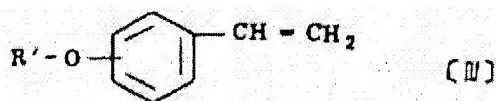
More specifically, the present invention pertains to a method for preparing 2-(substituted phenyl) propionic acid represented by General Formula [I] presented in the foregoing or an alkyl ester thereof, said method comprising the following steps I and II:

(I) a step of dehydrogenating a substituted phenyl ethane represented by General Formula [II]:



(in which R' represents a phenyl group or a methyl group)

at 400 to 700 °C in the presence of a dehydrogenation catalyst so as to prepare a substituted phenyl ethylene represented by General Formula [III]:

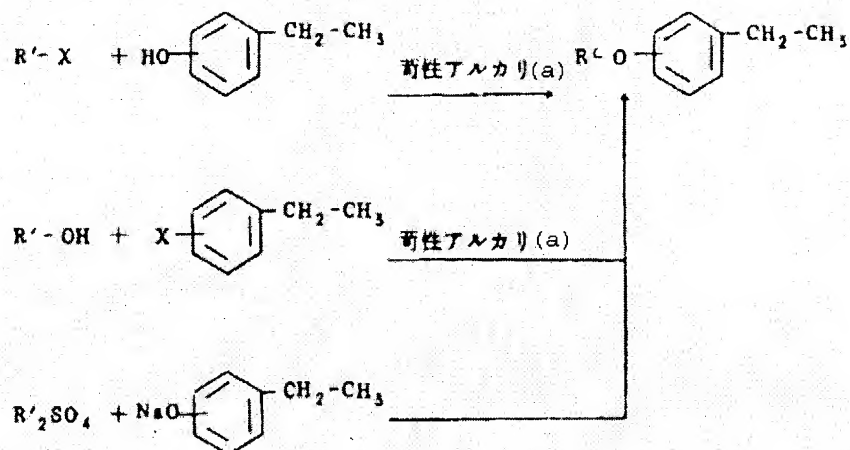


(in which R' has the same meaning as defined in the foregoing) and (II) a step of reacting the aforesaid substituted phenyl ethane with carbon monoxide and with water or a lower alcohol in the presence of a palladium-based catalyst so as to prepare the aforesaid 2-(substituted phenyl) propionic acid or an alkyl ester thereof.

Therefore, according to the present invention, 2-(substituted phenyl) propionic acid or an alkyl ester thereof can be obtained easily from substituted phenyl ethane, carbon monoxide, and water or a lower alcohol, which are raw materials that can be obtained inexpensively from the viewpoint of industrial production and in large quantities, through only two process steps.

The substituted phenyl ethane represented by the aforesaid General Formula [II], which is the starting material of the present invention, is, specifically speaking, 3-phenoxy phenyl ethane, 4-phenoxy phenyl ethane, 2-phenoxy phenyl ethane, 3-methoxy phenyl ethane, 4-methoxy phenyl ethane, or 2-methoxy phenyl ethane. These substituted phenyl ethanes can be produced by any known conventional methods. As an example of the conventional synthesis methods, the

method shown below is known, and the target substances can be synthesized easily from inexpensive materials.



Key: a) caustic alkali.

(R' = a phenyl group or a methyl group; X = Cl, Br, or I)

The following explains the method for implementing each process step in concrete terms.

The objective of Process Step I, which is the first-stage reaction in the method of the present invention, is to obtain a substituted phenyl ethylene represented by General Formula [III] presented in the foregoing by dehydrogenation of substituted phenyl ethane represented by General Formula [II] presented in the foregoing.

The substituent of the substituted phenyl ethane used in the present invention bonds with a phenyl group by means of an oxygen atom and is, consequently, susceptible to transition or detachment. In addition, with phenyl alkanes having this kind of substituent, their alkyl groups are, in general, prone to detach. Therefore, for Process

Step I, it is essential to select a method that does not cause the transition or elimination of said substituent and ethyl group.

The present inventors researched extensively about this type of dehydrogenation reaction of substituted phenyl ethanes and, as a consequence, learned that the objective could be achieved by carrying out the reaction according to the method that produces alkenyl phenols by dehydrogenation of alkyl phenols. The method for dehydrogenating alkyl phenols is disclosed in JP-B-S49-041183, JP-B-S53-043491, JP-A-S54-055529, JP-A-S55-028958, JP-A-S57-203022, JP-A-S61-293942, etc., and, thus, it has been known. That is, Process Step I of the present invention is preferably implemented according to this type of dehydrogenation method of alkyl phenols. As the dehydrogenation catalyst, iron oxide, zinc oxide, magnesium oxide, chromium oxide, tin oxide, titanium oxide, barium oxide, etc., for example, can be used singly or as a mixture. The reaction temperature is usually from 400 to 700 °C, preferably from 450 to 650 °C. The feed rate of the raw material is usually selected from the range of 0.1 to 10 hr⁻¹ liquid hour space velocity (LHSV) based on the catalyst. The reaction may be carried out either under atmospheric pressure, reduced pressure, or a pressurized condition, but it is practical to carry out the reaction under atmospheric pressure or thereabouts. The dehydrogenation reaction can be implemented advantageously with a lower partial pressure from the viewpoint of equilibrium, and it is usually carried out in the presence of a diluent. As the diluent, water, benzene,

toluene, nitrogen gas, carbon dioxide gas, etc., are used. The amount of the diluent used here is 2 to 200 moles, preferably 3 to 100 moles, per 1 mole of the raw material. When a liquid substance, such as water, etc., is used as the diluent, the resulting product has the diluent mixed in it; therefore, part or all of it is eliminated as necessary.

The dehydrogenation reaction product obtained in this manner is a mixture that consists of unchanged substances and some amount of by-products besides the target substance, that is, substituted phenyl ethylene, of the present step, and this mixture can be put to the subsequent process step II as it is or after the substituted phenyl ethylene is condensed or purified.

Process Step II is a step for obtaining 2-(substituted phenyl) propionic acid or an alkyl ester thereof from the substituted phenyl ethylene obtained by the aforesaid process step I. This method can be implemented according to a known carbonylation method according to which an olefinic unsaturated compound is reacted with carbon monoxide and with water or a lower alcohol in the presence of a palladium-based catalyst. The use of water here yields a 2-(substituted phenyl) propionic acid, while the use of a lower alcohol yields an alkyl ester corresponding to it.

As the palladium-based catalyst employed here, palladium complexes are suitable, and palladium complexes having a palladium atomic value of from 0 to 2 and having, as the ligand, a halogen atom, trivalent phosphorous compound, π -allyl group, amine, nitrile, oxime, /32

olefin, carbon dioxide, etc., are effective. Concrete examples include bistriphenyl phosphine dichloro palladium, bistributyl phosphine dichloro palladium, bistricyclohexyl phosphine dichloro palladium, π -allyl triphenyl phosphine chloro palladium, triphenyl phosphine piperidine dichloro palladium, bisbenzonitrile dichloro palladium, biscyclohexyl oxime dichloro palladium, 1,5,9-cyclo dodeca triene-dichloro palladium, bistriphenyl phosphine dicarbonyl palladium, bistriphenyl phosphine palladium acetate, tetrakis triphenyl phosphine palladium, etc. These need not be isolated in the form of palladium complexes for the use as the catalyst of the present invention, and it is possible to use compounds that can form the aforesaid complexes in the reaction system. More specifically, the present invention can employ a method that brings both a palladium salt, such as palladium oxide, palladium sulfate, palladium chloride, etc., and a compound that can become a ligand, such as phosphine, nitrile, an allyl compound, amine, oxime, olefin, carbon dioxide, etc., into the reaction system simultaneously.

Some examples of the phosphine here include triphenyl phosphine, tritolyl phosphine, tributyl phosphine, triethyl phosphine, etc. Some examples of the nitrile include benzonitrile, propionitrile, etc. Some examples of the allyl compound include allyl chloride, allyl alcohol, etc. Some examples of the amine include benzyl amine, pyridine, etc. Some examples of the oxime include cyclohexyl oxime, acetoxime, etc. Some examples of the olefin include 1,5-cyclo octadiene, 1,5,9-cyclo

dodeca triene, etc. The addition amount of these compounds that can become ligands is 0.8 to 10 moles, preferably 1 to 4 moles, per 1 gram atom of palladium.

The quantity of palladium used in the reaction is 0.0001 to 0.5 gram atom, preferably 0.001 to 0.1 gram atom, per 1 mole of the substituted phenyl ethylene. The aforesaid type of palladium-based catalyst can exhibit its activity without the use of a catalyst aid, but, for the purpose of further improving the reaction speed, hydrogen chloride, boron trifluoride, iodine, etc., may be added as catalyst aids in a trace amount.

The lower alcohol used for the method of the present invention is not limited in any specific way, and some examples of it include methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, sec-butanol, etc. Alcohol and water are reaction materials and also function as solvents, and they are used in a quantity of 0.5 to 50 parts by weight, preferably 1 to 20 parts by weight, per 1 part of the substituted phenyl ethylene.

↑
C₁₂H₂₂

The carbonylation reaction is carried out at a reaction temperature of 40 to 200 °C, preferably 60 to 150 °C, under a pressure of 30 to 400 kg/cm², preferably 50 to 300 kg/cm², created by carbon monoxide.

Generally speaking, it is sufficient to continue the reaction until the absorption of carbon monoxide becomes no longer observable,

and a reaction time of 1 to 10 hours can produce the target substance at a satisfactory yield.

The carbonylation reaction of the substituted phenyl ethylene of the present process generates not only the target substances, that is, 2-(substituted phenyl) propionic acid and an alkyl ester thereof, but also its isomer 3-(substituted phenyl) propionic acid and an alkyl ester thereof in small quantities, but these can be easily separated by a conventional distillation operation. Furthermore, the recovered catalyst can be reused for the carbonylation reaction.

[Effects of the Invention]

The method of the present invention uses inexpensive raw materials compared with conventional methods, and each of its process steps can be implemented with a simple operation without the need for handling complex intermediates or special chemical agents.

Since Process Step I of the present invention achieves dehydrogenation without the use of an oxidizing agent, it requires no special treatment and equipment from the standpoint of handling, thus rendering itself economical. In addition, when the substituted phenyl ethane obtained in Process Step I is used for the carbonylation reaction of Process Step II, the target substance can be obtained at a high yield, and, since the impurity content is small, refining is easier to implement; thus, the method of the present invention is advantageous for preparing pharmaceuticals or intermediate materials /330 thereof, which must have high purity.

As explained in the foregoing, the novel method of the present invention makes it possible to produce 2-(substituted phenyl) propionic acid or an alkyl ester thereof with simple operations and at a high yield as well as effectively and economically.

[Working Examples]

The present invention will hereinafter be described in further detail by the following working examples. It should, however, be borne in mind that the present invention is not limited to or by these examples.

Working Example 1

Process Step I: Into a dehydrogenation reactor filled with 300 mL of a tin oxide catalyst, 3-phenoxy phenyl ethane, together with water in a quantity that was 10 times the moles of the 3-phenoxy phenyl ethane, was fed at an LHSV of 0.5 hr^{-1} , and a dehydrogenation reaction was carried out under atmospheric pressure at 580°C . The analysis of the obtained product by gas chromatography revealed that the conversion rate of the 3-phenoxy phenyl ethane was 61.3% and the selectivity to 3-phenoxy phenyl ethylene was 96.3%. After water was separated from this reaction solution, the remaining solution was put to the next process step II.

Process Step II: 100 g of the aforesaid dehydrogenation reaction solution from which water had been eliminated, 250 g of isopropyl alcohol, 1.0 g of bistriphenyl phosphine dichloro palladium, 0.5 g of triphenyl phosphine, and 0.5 g of 35% hydrochloric acid were charged

into a 1,000 mL-capacity autoclave, and, while the autoclave was pressurized to 120 kg/cm² with carbon monoxide, the reaction system was reacted at 110 °C for 3 hours.

After the autoclave was cooled to room temperature and the residual gas was released, the product was analyzed by gas chromatography according to the internal standard method, and the conversion rate of the 3-phenoxy phenyl ethylene was found to be 99.8%, the selectivity to 2-(3-phenoxy phenyl) propionic acid isopropyl ester was found to be 93.2%, and the selectivity to 3-(3-phenoxy phenyl) propionic acid isopropyl ester was found to be 6.4%.

The aforesaid reaction solution was distilled under reduced pressure, thereby obtaining 2-(3-phenoxy phenyl) propionic acid isopropyl ester, and its structure was examined by NMR.

NMR (TMS, CDCl₃) δ (ppm): 1.13-1.23 (dd, 6H), 1.46 (d, 3H), 3.66 (q, 1H), 5.00 (m, 1H), 6.90-7.39 (m, 9H)

Working Example 2

Process Step I: Into the same dehydrogenation reactor as the one used in Working Example 1, 4-phenoxy phenyl ethane, together with benzene in a quantity that was 10 times the moles of the 4-phenoxy phenyl ethane, was fed at an LHSV of 0.5 hr⁻¹, and a dehydrogenation reaction was carried out under atmospheric pressure at 530 °C. The resulting conversion rate of the 4-phenoxy phenyl ethane was 20.5%, and the selectivity to 4-phenoxy phenyl ethylene was 95.3%. After

benzene was distilled away from this reaction solution under reduced pressure, the remaining solution was put to the next process step II.

Process Step II: 100 g of the aforesaid dehydrogenation reaction solution from which benzene had been eliminated, 250 g of sec-butanol, 1.0 g of bistriphenyl phosphine dichloro palladium, and 0.2 g of a 30% boron trifluoride ether complex were charged into a 1,000 mL-capacity autoclave, and, while the autoclave was pressurized to 80 kg/cm² with carbon monoxide, the reaction system was reacted at 70 °C until the absorption of carbon dioxide became no longer observable.

The analyses of the obtained reaction solution revealed that the resulting conversion rate of the 4-phenoxy phenyl ethylene was 99.8%, the selectivity to 2-(4-phenoxy phenyl) propionic acid sec-butyl ester was 92.6%, and the selectivity to 3-(4-phenoxy phenyl) propionic acid sec-butyl ester was 7.0%.

Working Example 3

Process Step (I): Into the same dehydrogenation reactor as the one used in Working Example 1, 3-phenoxy phenyl ethane, together with benzene in a quantity that was 10 times the moles of the 3-phenoxy phenyl ethane, was fed at an LHSV of 0.3 hr⁻¹, and a dehydrogenation reaction was carried out under atmospheric pressure at 560 °C. The resulting conversion rate of the 3-phenoxy phenyl ethane was 57.1%, and the selectivity to 3-phenoxy phenyl ethylene was 94.1%.

Process Step II: 50 g of the aforesaid dehydrogenation reaction solution containing benzene, 30 mL of a 10% aqueous solution of

hydrochloric acid, and 0.5 g of bistriphenyl phosphine dichloro palladium were charged into a 200 mL-capacity autoclave, and, while the autoclave was pressurized to 200 kg/cm² with carbon monoxide, the reaction system was reacted at 120 °C until the absorption of carbon dioxide became no longer observable. After the reaction system was /331 cooled to room temperature, the reaction solution was mixed with sodium carbonate to implement alkali extraction, thereby separating a benzene layer, after which the extracted solution was made acidic with hydrochloric acid and extracted with ether. The ether layer was washed with water and dried over magnesium sulfate, and ether was distilled away, thereby obtaining 5.1 g of 2-(3-phenoxy phenyl) propionic acid.

Working Example 4

Process Step (I): Into the same dehydrogenation reactor as the one used in Working Example 1, 4-methoxy phenyl ethane, together with water in a quantity that was 10 times the moles of the 4-methoxy phenyl ethane, was fed at an LHSV of 0.3 hr⁻¹, and a dehydrogenation reaction was carried out under atmospheric pressure at 490 °C. The resulting conversion rate of the 4-methoxy phenyl ethane was 18.8%, and the selectivity to 4-methoxy phenyl ethylene was 92.0%. After water was separated from this reaction solution, the remaining solution was put to the next process step II.

Process Step II: 100 g of the aforesaid dehydrogenation reaction solution from which water had been eliminated, 250 g of sec-butanol, 1.0 g of bistriphenyl phosphine dichloro palladium, 0.5 g of triphenyl

phosphine, and 0.5 g of 35% hydrochloric acid were charged into a 1,000 mL-capacity autoclave, and, while the autoclave was pressurized to 120 kg/cm² with carbon monoxide, the reaction system was reacted at 110 °C until the absorption of carbon monoxide became no longer observable.

The analyses of the obtained reaction solution revealed that the resulting conversion rate of the 4-methoxy phenyl ethylene was 99.0%, the selectivity to 2-(4-methoxy phenyl) propionic acid sec-butyl ester was 93.0%, and the selectivity to 3-(4-methoxy phenyl) propionic acid sec-butyl ester was 5.9%.

Working Example 5

Process Step (I): Into the same dehydrogenation reactor as the one used in Working Example 1, 3-methoxy phenyl ethane, together with benzene in a quantity that was 10 times the moles of the 3-methoxy phenyl ethane, was fed at an LHSV of 0.3 hr⁻¹, and a dehydrogenation reaction was carried out under atmospheric pressure at 560 °C. The resulting conversion rate of the 3-methoxy phenyl ethane was 58.8%, and the yield of 3-methoxy phenyl ethylene to the converted 3-methoxy phenyl ethane was 93.9%. This reaction solution was distilled, thereby obtaining a fraction comprised of 68% of 3-methoxy phenyl ethylene and 32% of 3-methoxy phenyl ethane.

Process Step II: A reaction was carried out in the same manner as in Process Step II of Working Example 1, except that 100 g of the aforesaid fraction was used in this case. The resulting conversion

rate of the 3-methoxy phenyl ethylene was 99.8%, the selectivity to 2-(3-methoxy phenyl) propionic acid isopropyl ester was 93.2%, and the selectivity to 3-(3-methoxy phenyl) propionic acid isopropyl ester was 6.3%.